A few attempts to increase the amount of a drug coated onto the microneedles

Ling Liang

Beijing University of Chemical Technology

Yang Chen

Beijing University of Chemical Technology

Gui Yao Ren

Beijing University of Chemical Technology

Jun You Li

Beijing University of Chemical Technology

Xin Dong Guo (✉ xdguo@buct.edu.cn)

Beijing University of Chemical Technology <https://orcid.org/0000-0001-5581-4253>

Research Article

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Abstract

As an approach of painless administration, coated microneedles (MNs) have an increasing attention on the drug loading capacity to meet higher drug dosage requirement. In this work, the solid and coated MNs were successfully fabricated using hot-compaction process and dipping with a dam board reservoir. The maximum drug loading of different height, arrays and coating solutions reached 118 μg , which was hundreds of times the unmodified coated MNs. The in vitro drug delivery was also evaluated and the result revealed that the coated MNs fabricated could achieve about 90% drug delivery efficiency. The insulin-coated MNs holding 0.5 IU of insulin were fabricated with dipping method, which had the same therapeutic effect on diabetic mice compared with the injection of the same dose. All the results demonstrated that coated MNs could meet the dosage needs of diseases by improving the height, arrays and coating solutions.

1. Introduction

Coated MNs have been a promising and attractive medical tool for painlessly delivering a wide range of active drugs into the skin. In previous studies, different drugs, such as vaccine [1-4], desmopressin [5], human growth hormone [6], salmon calcitonin [7], lidocaine [8, 9] and DNA [10-13], are rapidly delivered into the skin using coated MNs due to the superior insertion ability. Moreover, the coating drugs on the MNs may prolong the long-term stability when the active drugs are stored in a solid state [3, 14-20]. A study demonstrates that the M2e5x VLP-coated MNs can maintain the M2e antigenicity and immunogenicity for 8 weeks at room temperature [21].

These advantages make coated MNs have the promising carrier to painlessly deliver drugs into the skin. However, the application and development of coated MNs are limited due to the uniformity and amount of drug loading. To fabricate coated MNs with homogeneous drug dose, several approaches have been proposed gradually. In the inkjet printing process, the drug loading is controlled by adjusting the size of droplets [15]. In another study on coated MNs, the drug loading is controlled by changing the height of these coating layers while dipping the coating solutions [16]. Unfortunately, another difficulty, low drug dose still puzzles people. Some people increased the drug loading of coated MNs by increasing the number of dipping [22, 23]. A study on coated MNs showed that the drug dose of hemagglutinin antigen is only 140 ng per needle even the concentration of hemagglutinin antigen is up to 25 mg/mL [3]. Moreover, the drug dose is only 10 ng or about 100 ng per needle in some studies [5, 24-26]. Obviously, low drug loading cannot reach dose requirements during the application.

To improve the drug loading of coated MNs, increasing the dipping times and coating height in the fabrication process are the main solutions. After dipping these coating solutions several times, the drug loading may be improved in different degrees. However, it is hard to fabricate coated MNs with homogeneous drug loading. In addition, the MN tips cannot penetrate the skin due to the cover of loaded thick coating layers. Nowadays, to improve the loaded drug dose, another approach is increasing coating height even covering the whole MN patch with the coating layer. However, in the skin penetration

experiment, only a part of MN body can insert into the skin due to the elastic property of the skin. Only a part of drugs can be delivered to the subcutaneous tissue. As a result, the drug delivery efficiency is low. Moreover, precise control of drug delivery in the process is still a challenge. Therefore, fabricating coated MNs with high drug loading, homogeneous drug loading and high drug delivery efficiency puzzle people all the time.

To overcome these drawbacks and fabricate coated MNs with high drug loading, a dip-coating process is proposed. As described previously [27], polylactic acid (PLA) was chosen to fabricate the solid MNs using the hot-compaction process. Coating formulation was the key to increase the drug loading. First, several additives were dissolved in deionized (DI) water to prepare solutions. Afterwards, these formulations formed by uniformly mixing the solutions with drugs. In the dip-coating process, a 300 μm -tall dam board was adhered to the reservoir to unify the height of coating layers. By immersing PLA MNs with coating formulations, coated MNs with high drug loading were fabricated. The effects of coating formulations and MN height on drug loading on MN tips were studied detailedly. Coated MNs were inserted into the porcine cadaver skin to determine the ability to deliver numerous drugs. *In vivo* pharmacokinetic studies in mice were conducted to evaluate the feasibility that coated MNs were used to treat diabetes. The result showed that insulin-coated MN and subcutaneous injection have the same therapeutic effect on diabetic mice.

2. Materials And Methods

2.1 Materials

Polyvinyl alcohol (PVA, MW 6000) was obtained from ACROS Organics, Geel, Belgium. Polydimethylsiloxane (PDMS, Sylgard 184) was purchased from Dow Corning, Midland, MI). Other chemicals include sucrose (Sigma-Aldrich, St Louis, MO), sulforhodamine B (MW 559 Da, Sigma Aldrich) and polylactic acid particles (PLA, 1.0 dL/g, Birmingham Polymer, Pelham, AL). Female BALB/c mice were obtained from the Institute of Laboratory Animal Sciences (ILAS). Two weeks before the experiment, the mice were made diabetics by injecting streptozotocin (STZ, Sigma-Aldrich, St Louis, Mo, USA, 50 mg/kg BW). Insulin was purchased from Jiangsu Wanbang Pharm. Company (Xuzhou, China). Porcine cadaver skins purchased from a local slaughterhouse was utilized in vitro test.

2.2 Fabrication of PLA MNs

Using the method mentioned previously [28], solid MNs were fabricated from PLA particles using the hot-compaction process. First, PLA particles was placed on the PDMS mold and heated in vacuum drying oven (Biocool, Pilot1-2LD, China) for 40 min at 200 °C. Then, press the molten PLA and cool to room temperature. In order to prepare the desired solid MNs, the PDMS molds with different hole heights (550 μm , 650 μm and 750 μm) and hole arrays (5 $\times$ 5, 8 $\times$ 8, 10 $\times$ 10, 11 $\times$ 11, 15 $\times$ 15) were fabricated. Finally, solid MNs with heights of 550 μm , 650 μm and 750 μm and arrays of 5 $\times$ 5, 8 $\times$ 8, 10 $\times$ 10, 11 $\times$ 11, 15 $\times$ 15 were fabricated.

2.3 Coating formulations

In order to assure the drug loading, the drug was mixed with the coating solution in different ratio. The coating solution was composed of 7.7% PVA (w/w), 15.4% sucrose (w/w) and 76.9% deionized (DI) water (w/w). Sulforhodamine B was selected as a model drug. The weight ratio of coating solution to model drug was 2:0.5, 2:0.75, 2:1 and 2:1.25, respectively (formulation listed in Table 1).

Table.1. Coating formulations for the preparation of coated polymer MNs.

Formulation ID	I	II	III	IV
Solution-solid ratio (w/w)	2:0.5	2:0.75	2:1	2:1.25

The solution contained 7.7 % PVA, 15.4 % sucrose and 76.9 % DI water (wt,%). The solid was sulforhodamine B.

2.4 Fabrication of coated MNs

To fabricate coated MNs with high drug loading, a dip-coating device was used as mentioned before [29]. First, the reservoir was filled with the coating solution until the liquid level was tangent to the top of the reservoir. Then, the 300 μm -tall dam board was adhered to the top of the reservoir (simply described as dam board reservoir) so that the coating layer was 300 μm away from the base of the MN. The portable holder was moved down until the MN patch touching the dam board, maintaining for 10 s, as shown in Figure 1A. Finally, the fabricated coated MNs were dried in vacuum drying oven at 25°C for 12 h for later use. All microneedle images were taken by the stereomicroscope (SZX7, Olympus, Japan).

2.5 *In vitro* skin insertion test

To determine the application effect of coated MNs with high drug loadings, the MN patch was used to manually insert the porcine cadaver skin. Before the insertion test, the hair on the skin surface was removed using a stainless razor. Afterwards, the skin was sprayed with 75% ethanol to wipe off the dirt on the surface. The dried coated MNs were manually inserted into the porcine cadaver skin and left for 2 min. After withdrawal, the used coated MN patch and skin were pictured using a stereomicroscope (SZX7, Olympus, Japan). To observe the depth of drug in the skin tissue, the skin was sliced and pictured.

2.6 Measurement of drug loading and drug delivery efficiency

To fabricate coated MNs with high and homogeneous drug loading, the different formulations of coating solution were coated. The amount of sulforhodamine B coated on the PLA MNs (n = 10) was determined by a microplate reader (Fluoroskan Ascent®, Thermo Scientific, China). Briefly, sulforhodamine B coated on the MNs was dissolved in DI water. Then, 100 μl of the extracted solution and standard solution were injected into the 96-well plate. We could calculate out the drug loading of sulforhodamine B by measuring the fluorescence intensity according to a calibration curve constructed from different concentrations

sulforhodamine B solutions. In a same method, the residual amount of sulforhodamine B was measured by dissolving coated MNs removed after inserting the skin for 2 min in DI water. The mass of sulforhodamine B left behind on the skin surface was estimated by applying tape (Scotch super 33, McMaster-Carr). Dissolve the material removed by the tape in deionized water, and calculate the residual amount of drug on the skin surface according to the fluorescence intensity. The calculation result showed that there was almost no residual amount, so this part was ignored. Finally, the drug delivery efficiency was calculated by dividing the amount delivered into the skin by the amount of non-inserted MNs.

2.7 *In vivo* transdermal delivery via insulin-coated MNs

A mouse model (BALB/c female mice, 16~18 g) of type 1 diabetes was created as mentioned in prior experiment [28]. First, dry STZ powder was dissolved in sodium citrate buffer (pH 4.5) and the concentration was 10 mg/mL. Afterwards, healthy mice were injected STZ with a dose of 200 mg/Kg by intraperitoneal injection. Before injection of STZ, mice were fasted overnight but could receive water. Finally, after 72 h, the diabetic mice models were successfully created when the blood glucose (BG) level reached to 300-550 mg/dL monitored with a One Touch glucometer (LifeScan, Inc., Milpitas, CA, USA).

To test the transdermal delivery ability of coated MNs with high drug loading, insulin-coated MNs were fabricated. The coated solution and fabrication method were the same as the section 2.3 and 2.4 except that the model drug was replaced by insulin. The solution and insulin were mixed in a ratio of 3/1 by weight, so that each coated MN patch had 0.5 IU insulin. For comparison, 50 μ L of solution containing 0.5 IU insulin was injected in the injection group. Before MN administration, the back of the mice was shaved. And coated MNs with 0.5 IU insulin were inserted into the back skin of mice to test the treatment effect.

To continuously determine the blood glucose level, 5 μ L of blood samples were tested at different time intervals after delivering insulin to mice. The blood glucose level was tested at 0 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 5 h, 5.5 h, 6 h, 7 h and 8 h after delivering insulin. During blood glucose monitoring, the mice were fasted and deprived water.

3. Results And Discussion

3.1 Fabrication of coated MNs with high drug loading

Poly(lactic acid) (PLA) was elected as the solid MN materials because of its biocompatibility and biodegradability. The different heights and arrays solid MNs were fabricated by changing the size of the PDMS mold with the hot-compaction process. In this process, the solid MNs with the height of 550 μ m, 650 μ m and 750 μ m were prepared. The main factor that restricts the drug loading was the drug content in coating solution and the size of the MNs. In this study, the coating solution was prepared by changing the ratio of the model drug to the liquid to increase the drug content. Figure 1B1 and 1B2 are partial enlarged images of solid MN and coated MN, respectively, to observe the shape of MN more clearly. Figure 1C1-1C3 showed coated MNs with the coating formulation $\square$ and height of 550, 650 and 750 μ m.

Figure 1D1-1D4 showed coated MNs with the coating formulation Ⅱ and height of 550 μm . These images indicated that the coating method of Figure 1A can be used to uniformly coat different concentrations of coating solutions on MNs of different heights.

3.2 *In vitro* insertion capability

In Chen's works [29], the solid polymer microneedles used are the same as this study. The mechanical property of solid MN and coated MN were measured by a dynamometer. The mechanical properties curves of both MNs almost coincide, indicating that the coating will not affect the mechanical properties of the MNs and the MNs have sufficient mechanical properties. The solid MN was pierced into 8 layers of parafilm (each layer has a thickness of 127 μm). The MN could pierce through 4 layers of parafilm, and the fifth layer of parafilm could see obvious indentations, but there were no pierced holes. The result indicated that the MN has enough mechanical properties to penetrate the parafilm with a thickness of 508 μm . Images of the pierced parafilm were not collected at the time.

It is important to prepare coating formulations that not only adhere to MNs, but adhere to them during bypass the stratum corneum and insertion into the skin. However, in order to increase the drug loading, the amount of thickener was decreased, which leads to the decrease of the adhesion between the coating solution and MN. It may cause the coating to fall off when the coated MN inserted into the skin, making the drug delivery efficiency reduce.

In this study, the solid MN (Figure 2A1) and coated MNs (Figure 2A2) with the coating formulation Ⅱ, the height of 650 μm and the array of 5×5 were prepared. To determine the insertion capability and the transdermal drug delivery *in vitro*, the coated MN was inserted into porcine cadaver skin for 2 min. After inserting and removing, surface examination of the treated skin showed an array of red dots corresponding to sites of MN insertion and coating deposition from the array (Figure 2B1 and 2B2). These red dots that remained on the skin indicated the successful penetration of MNs into skin. Almost no residue was observed on the solid MN, as shown in Figure 2A2, indicating delivery of the drugs into skin. In Figure 2C1 and 2C2, the distance (350 μm) of the parallel dotted lines indicated the depth of the MN insertion, indicating that all the drugs on the MNs were delivered into the skin without falling off. Taken together, consequently, the coated MN arrays with high drug loading showed excellent performance *in vitro* skin insertion, which suggested these MNs were an effective means of transdermal delivery of drugs.

3.3 Determination of drug loadings and drug delivery efficiency

In order to prepare coated microneedles with high drug loading and high drug-loading efficiency, the two crucial parameters of drug loading and drug delivery efficiency were evaluated. In this study, different heights (550 μm , 650 μm , 750 μm) PLA MNs were successfully fabricated with hot-compaction process by changing the cavity depth of the PDMS mold. The coating formulation Ⅱ were chosen to fabricate the different heights (550 μm , 650 μm , 750 μm) coated microneedles corresponding to coating layer heights of 250 μm , 350 μm , 450 μm by using the 300 μm dam board, as shown in Figure 3B. Chen et al. [29] also

fabricated sulforhodamine-coated MNs with heights of 550 μm , 650 μm , and 750 μm , and their drug loadings of single MN were 12 ng, 14 ng, and 18 ng, respectively. As shown in Figure 3A, the amount of drug loadings of single MN was 450 ng, 570 ng and 750 ng, respectively, which is about 40 times the drug loading of the coated MNs prepared by Chen [29]. Compared with the increase of height of the coated microneedle, the amount of the drug loading does not increase proportionally, which is related to the higher the height of the microneedle and the smaller the diameter of the upper side. The drug delivery efficiency of different height microneedles was approximately 90%, which was as same as that of Chen's preparation of MNs, indicating that it has no great relationship with the height and drug loadings of the MNs.

In addition, the coating formulation was a vital factor during the fabrication of the high drug loading coated microneedles. In this part, the height of 650 μm of the solid microneedle were chosen. As shown in Figure 4A, the amount of the drug loading of the single coated MN coated with the coating formulation $\square$, $\square$, $\square$, $\square$ were 260 ng, 470 ng, 570 ng and 770 ng, respectively. As the concentration of the drug in coating formulation increased, the amount of drug loading increased. However, the viscosity of the coating solution decreased with the increase of the drug loading, resulting in a decreased adhesion of the coating solution on the MNs and a decreased drug delivery efficiency, which could attribute to a decrease in PVA and sucrose content in percentage, as shown in Figure 4A. Figure 4B showed coated MNs coated with coating formulations $\square$ - $\square$. It can be clearly seen that as the concentration of the coating solution increases, the thicker the coating layer.

3.4 Large-scale fabrication of MNs with high drug loadings

In order to further increase the drug loading, another measure we took was to change the array of the MNs. In this section, the coating formulation of $\square$, the height of 650 μm , the arrays of 8×8 , 10×10 , 11×11 and 15×15 were chosen. The coated MNs with high drug loadings were fabricated with dipping method, as shown in Figure 5A-D. The drug was uniformly distributed in the upper part of the MNs, indicating that the increase of the MN array will not affect the distribution of the coating solution. Figure 5E showed the drug loading of the whole MN patch with different arrays. The drug loading of each MN patch is 36 μg , 45 μg , 56 μg , and 118 μg , corresponding with arrays of 8×8 , 10×10 , 11×11 , and 15×15 . Serpe et al. [30] fabricated sulforhodamine-coated MNs with a height of 700 μm , drug loading of 15 μg and 57 needles, and drug loading of single needle was 263 ng. The drug loading of single needle with an array of 8×8 is 562.5 ng, which is more than twice that of Serpe [30]. Although the MN array reached 15×15 , the area of the MN patch was only 1 cm^2 , indicating that the MN array can be appropriately increased to increase the drug loading, thereby achieving the purpose of treatment. For example, for the treatment of some skin diseases such as psoriasis, under the premise of increasing the drug loading, the MN array can be appropriately increased to increase the treatment area [31].

3.5 *In vivo* pharmacokinetic studies in mice

To evaluate the effect of coated MNs in the treatment of diabetic mice, the insulin-loaded MNs were prepared. First, the solution containing 14.3% PVA, 14.3% sucrose and 71.4% DI water (wt.%) was prepared. Then, the insulin coating solution were prepared by mixing the insulin to the solution. The insulin-coated MNs holding 0.5 IU of insulin were fabricated with dipping method. To determine the *in vivo* efficacy of the prepared insulin-coated MNs, the insulin was delivered into the body of the diabetic mouse in the way of subcutaneous injection and insulin-coated MN. The insulin-coated MN were vertically and manually inserted into the skin for about 10 s and remained on the skin for 2 min.

Figure 6A showed the mouse back skin situation before and after MN administration. And the mice back skin has recovered after the insertion of insulin-coated MN for 1 h, indicating that the coated MN can provide a safe method for transdermal drug delivery. There are 25 clear pores on the mice skin, indicating that the insulin-coated coated MN successfully inserted into the skin. There were almost no residue on the MN after removal, indicating that the insulin were almost transferred into the skin (Figure 6B). Figure 6C showed the effect of blood glucose level after a subcutaneous injection and an administration of insulin-coated MN array. The “initial” is the blood glucose value detected at 0 h in Figure 6C at the beginning of the *in vivo* experiment. The ratio of the monitored blood glucose is the ratio of the monitored blood glucose to the initial value. The untreated mice remained hyperglycemic for eight hours. The blood glucose in mice treated with subcutaneous injection of 0.5 IU insulin quickly declined within 0.5 h and reached the stable value (15%) at 1.5 h for 3.5 h, returned to the initial value at 8 h, a similar blood glucose level profile was observed in mouse treated with the same dose of insulin-coated MN arrays, confirming that the proposed MNs displayed a similar effect to subcutaneous injection on hypoglycemic administration. In a word, the use of the insulin-coated MN arrays for treatment of diabete provided useful information for future *in vivo* animal studies.

4. Conclusion

In summary, the different heights (550, 650 and 750 μm) and arrays (5×5 , 8×8 , 10×10 , 11×11 and 15×15) solid MNs and coated MNs were successfully fabricated with hot-compaction and dipping method, respectively. Then the *in vitro* insertion capability, drug loading, drug delivery efficiency and *in vivo* pharmacokinetic studies were investigated. After inserting into the skin with coated MN, clear red spots were left on the skin and the insertion depth was 350 μm , indicating that the coated MN had sufficient mechanical properties to insert into the skin and deliver drugs into the skin. Coated MNs with a height of 550, 650, 750 μm and array of 8×8 , 10×10 , 11×11 , and 15×15 had drug loading of 450 ng, 570 ng, 750 ng, 36 μg , 45 μg , 56 μg , and 118 μg , respectively. Coated MN with coating formulations $\square$ - $\square$ had drug loadings of 260 ng, 470 ng, 570 ng and 770 ng, respectively. The drug delivery efficiency of coated MNs reached 90% except that the coated MNs with coating formulation $\square$ had only 80%, due to the weak adhesion between the coating solution and the MNs. Insulin-coated MNs have the same therapeutic effect on diabetic mice compared with the injection of the same dose. To sum up, we could change the height, arrays and the concentration of coating solutions to increase drug loading of coated MNs to meet treatment needs and the coated MNs have potential to serve as a noninvasive and painless method to treat some diseases.

Declarations

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Authors' contributions

Ling Liang: Writing- Original draft preparation. **Yang Chen:** Methodology. **Gui Yao Ren:** Data curation. **Jun You Li:** Data Curation. **Xin Dong Guo:** Conceptualization, Project administration.

Declaration of Informed Consent or Animal Studies

All procedures of animal studies were conducted in accordance with the guidelines of China-Japan Friendship Hospital for care and use of laboratory.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no conflict of interest.

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Figures

Figure 1

Fabrication of coated MNs with high drug loadings. (A) Schematic diagram of process to fabricate coated MNs. The coated MNs were fabricated by (I) dipping and (II) drying. (B1) and (B2) are partial enlarged images of solid MN and coated MN, respectively. (C1-C3) Coated MNs with the coating formulation $\square$ and height of 550, 650 and 750 μm . (D1-D4) Coated MNs with the coating formulation $\square$ - $\square$ and height of 550 μm . The scale bar in Figure 1B2 = 200 μm .

Figure 2

In vitro insertion capability of coated polymer MNs into porcine cadaver skin. (A1) The coated MN patch before insertion. (A2) The coated MN patch after insertion. (B1) The bright field image of porcine skin after the coated MN patch insertion. (B2) The fluorescent image of porcine skin after the coated MN patch insertion. (C1) The side view of porcine skin imaged by bright field. (C2) The side view of porcine skin imaged by fluorescent field.

Figure 3

(A) Drug loading and drug delivery efficiency of coated polymer MNs. (B) Coated MNs with different heights and coating formulation $\square$.

Figure 4

(A) Drug loading and drug delivery efficiency of coated polymer MNs. (B) Coated MNs with the height of 650 μm and coating formulations I–IV.

Figure 5

Large scale arrays of 650 μm -tall coated MNs and the drug loadings. Coated MNs with arrays of (A) 8×8 , (B) 10×10 , (C) 11×11 and (D) 15×15 . (E) The drug loadings of different MN arrays.

Figure 6

(A) The back skin of mouse during the MN insertion. (B) Insulin-coated MNs before and after insertion. (C) Blood glucose level after a subcutaneous injection and an administration of insulin-coated MN array.